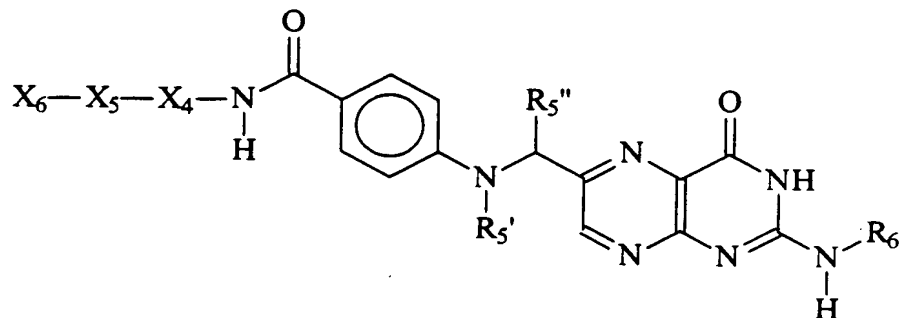


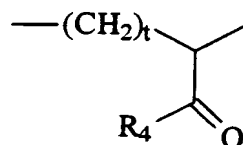
What is claimed is:

1. A compound of the formula:



wherein:

$X_4$  is  $-CH(X_4)$  or a group of formula:



5

$X_4$  is the side chain of a naturally-occurring or non-naturally-occurring amino acid, or a protected side chain of a naturally-occurring or non-naturally-occurring amino acid;

$X_5$  is  $-N(X_6)C(O)-$ ,  $-C(O)NH-$ ,  $-NHC(O)-$ ,  $-OC(O)NH-$ ,  
 10  $-C(S)NH-$ ,  $-SC(S)NH-$ ,  $-SC(O)NH-$ ,  $-OC(S)NH-$ ,  $-C(O)O-$ ,  
 $-C(O)(CH_2)_n-$  or a bond;

$n$  is an integer from 1 to 50;

each  $X_6$  and  $X_6$  is, independently, hydrogen or a  
 hydrocarbyl group selected from  $C_1$ - $C_{10}$  alkyl,  $C_2$ - $C_{10}$  alkenyl,  
 15  $C_2$ - $C_{20}$  alkynyl,  $C_6$ - $C_{14}$  aryl,  $C_6$ - $C_{14}$  aralkyl,  $C_3$ - $C_{14}$  cycloalkyl,  
 $C_5$ - $C_{14}$  fused cycloalkyl,  $C_4$ - $C_{14}$  heterocycle,  $C_4$ - $C_{14}$   
 heterocyclalkyl,  $C_4$ - $C_{14}$  heteroaryl and  $C_4$ - $C_{14}$  heteroarylalkyl;  
 wherein said hydrocarbyl group is substituted with at least  
 two hydroxyl groups, and is optionally substituted with oxo,  
 20 acyl, alkoxy, alkoxycarbonyl, alkyl, alkenyl, alkynyl, amino,  
 amido, azido, aryl, heteroaryl, carboxylic acid, cyano,  
 guanidino, halo, haloalkyl, haloalkoxy, hydrazino, ODMT,

alkylsulfonyl, nitro, sulfide, disulfide, sulfone, sulfonate, sulfonamide, thiol, and thioalkoxy; provided that  $X_6$  is not hydrogen;

$R_4$  is a hydroxyl group or a protected hydroxyl group;

5  $R_5$  is hydrogen,  $C_1$ - $C_{10}$  alkyl,  $C_2$ - $C_{10}$  alkenyl,  $C_3$ - $C_{20}$  alkynyl,  $C_6$ - $C_{14}$  aryl or an amino-protecting group

$R_{5'}$  is hydrogen,  $C_1$ - $C_{10}$  alkyl,  $C_2$ - $C_{10}$  alkenyl,  $C_2$ - $C_{20}$  alkynyl,  $C_6$ - $C_{14}$  aryl,  $C_6$ - $C_{14}$  aralkyl,  $C_3$ - $C_{14}$  cycloalkyl, formyl, aminoalkyl or hydroxymethyl;

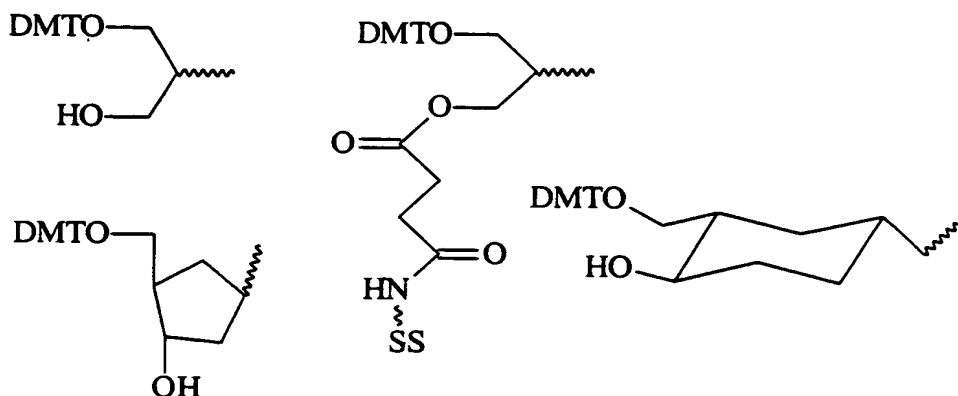
10  $R_6$  is hydrogen or an amino protecting group; and  
t is 1 or 2.

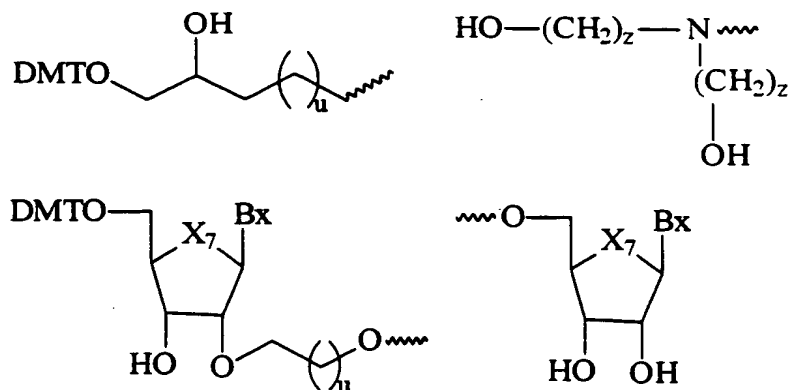
2. The compound of claim 1 wherein said amino acid is amino caproic acid.

3. The compound of claim 1 connected to an  
15 oligonucleotide by a disulfide group.

4. The compound of claim 1 wherein said  $X_4$  is the side chain of glutamic acid.

5. The compound of claim 1 wherein said  $X_6$  has one of the formulas:





wherein:

SS is a solid support;

X<sub>7</sub> is O or CH<sub>2</sub>;

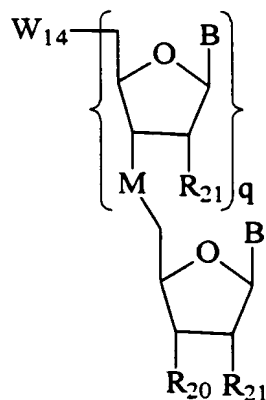
Bx is a nucleobase, C<sub>4</sub>-C<sub>14</sub> heterocyclyl or hydrogen;

z is an integer from 1 to 50; and

u is an integer from 2 to 5.

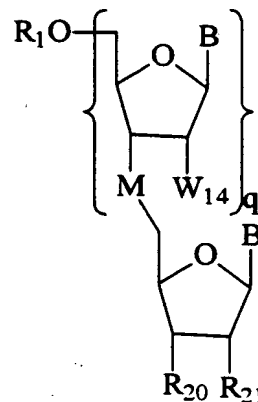
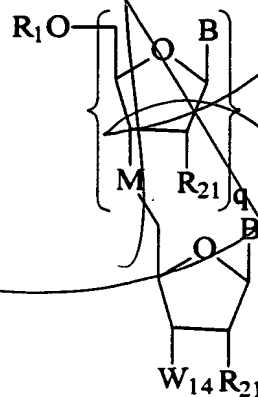
6. The compound of claim 1 wherein said X<sub>6</sub> is attached to a solid support.

7. A compound having formula XVIA, XVIB, XVIC or XVID:



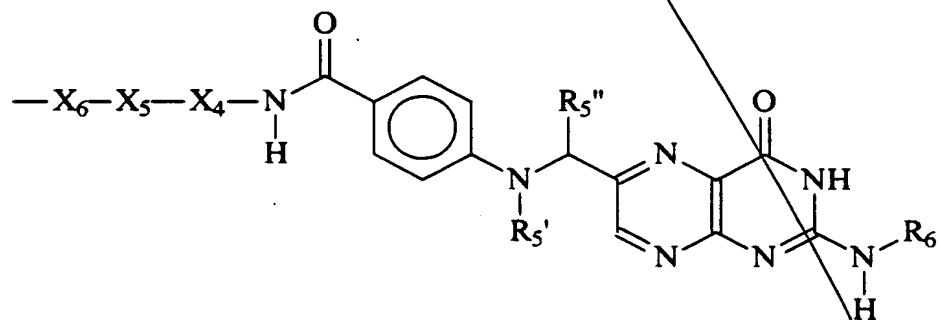
XVIA

XVIC



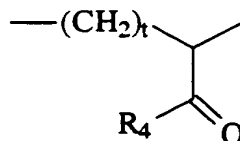
wherein:

$W_{14}$  has the formula:



wherein:

X<sub>4</sub> is -CH(X<sub>4</sub>,) or a group of formula:



$X_4$  is the side chain of a naturally-occurring or non-naturally-occurring amino acid, or a protected side chain of a naturally-occurring or non-naturally-occurring amino acid;

5  $t$  is 1 or 2;

$X_5$  is  $\text{---N(X}_6\text{)C(O)---}$ ,  $\text{---C(O)NH---}$ ,  $\text{---NHC(O)---}$ ,  $\text{---OC(O)NH---}$ ,  $\text{---C(S)NH---}$ ,  $\text{---SC(S)NH---}$ ,  $\text{---SC(O)NH---}$ ,  $\text{---OC(S)NH---}$ ,  $\text{---C(O)O---}$ ,  $\text{---C(O)(CH}_2\text{)}_n\text{---}$  or a bond;

$n$  is an integer from 1 to 50;

10 each  $X_6$  and  $X_6$  is, independently, a bond, hydrogen or a hydrocarbyl group selected from  $C_1\text{---}C_{10}$  alkyl,  $C_2\text{---}C_{10}$  alkenyl,  $C_2\text{---}C_{20}$  alkynyl,  $C_6\text{---}C_{14}$  aryl,  $C_6\text{---}C_{14}$  aralkyl,  $C_3\text{---}C_{14}$  cycloalkyl,  $C_5\text{---}C_{14}$  fused cycloalkyl,  $C_4\text{---}C_{14}$  heterocycle,  $C_4\text{---}C_{14}$  heterocyclalkyl,  $C_4\text{---}C_{14}$  heteroaryl and  $C_4\text{---}C_{14}$  heteroarylalkyl;

15 wherein said hydrocarbyl group is substituted with at least two hydroxyl groups, and is optionally substituted with oxo, acyl, alkoxy, alkoxycarbonyl, alkyl, alkenyl, alkynyl, amino, amido, azido, aryl, heteroaryl, carboxylic acid, cyano, guanidino, halo, haloalkyl, haloalkoxy, hydrazino, ODMT,

20 alkylsulfonyl, nitro, sulfide, disulfide, sulfone, sulfonate, sulfonamide, thiol, and thioalkoxy; provided that  $X_6$  is not hydrogen and  $X_6$  is not a bond;

$R_1$  is hydrogen or a hydroxyl protecting group;

$R_4$  is a hydroxyl group or a protected hydroxyl group;

25 each  $R_5$  and  $R_{40}$  is, independently, hydrogen,  $C_1\text{---}C_{10}$  alkyl,  $C_2\text{---}C_{10}$  alkenyl,  $C_2\text{---}C_{20}$  alkynyl,  $C_6\text{---}C_{14}$  aryl or an amino-protecting group

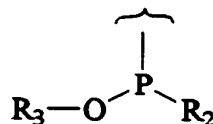
$R_5$  is hydrogen,  $C_1\text{---}C_{10}$  alkyl,  $C_2\text{---}C_{10}$  alkenyl,  $C_2\text{---}C_{20}$  alkynyl,  $C_6\text{---}C_{14}$  aryl,  $C_6\text{---}C_{14}$  aralkyl,  $C_3\text{---}C_{14}$  cycloalkyl, formyl, aminoalkyl or hydroxymethyl;

30

$R_6$  is hydrogen or an amino protecting group;

FOUO "T060600"

R<sub>20</sub> is hydrogen or a group of formula:



R<sub>2</sub> is -N(R<sub>7</sub>)<sub>2</sub>, or a heterocycloalkyl or heterocycloalkenyl ring containing from 4 to 7 atoms, and having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;

R<sub>7</sub> is straight or branched chain alkyl having from 1 to 10 carbons;

R<sub>3</sub> is a phosphorus protecting group;

10 R<sub>21</sub> is hydrogen, hydroxyl, fluoro or a group of formula Z-R<sub>22</sub>-(R<sub>23</sub>)<sub>v</sub>;

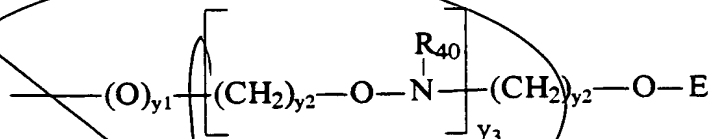
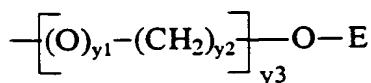
Z is O, S, NH or N-R<sub>22</sub>-(R<sub>23</sub>)<sub>v</sub>;

R<sub>22</sub> is C<sub>1</sub>-C<sub>20</sub> alkyl, C<sub>2</sub>-C<sub>20</sub> alkenyl, or C<sub>2</sub>-C<sub>20</sub> alkynyl;

15 R<sub>23</sub> is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, 20 disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleo- 25 tides;

or R<sub>21</sub> has one of the formulas:

FOOD T862600



wherein:

y<sub>1</sub> is 0 or 1;

each y<sub>2</sub> is, independently, 0 to 10;

5 y<sub>3</sub> is 1 to 10;

E is N(R<sub>41</sub>)(R<sub>42</sub>) or N=C(R<sub>41</sub>)(R<sub>42</sub>);

each R<sub>41</sub> and each R<sub>42</sub> is independently H, C<sub>1</sub>-C<sub>10</sub> alkyl, a  
nitrogen protecting group, or R<sub>41</sub> and R<sub>42</sub> taken together form a  
nitrogen protecting group; or R<sub>41</sub> and R<sub>42</sub> taken together with  
10 the N or C atom to which they are attached form a ring  
structure that can include at least one heteroatom selected  
from N and O;

B is a nucleobase;

M is an optionally protected internucleoside linkage;

15 q is from zero to about 50; and

v is from zero to about 10.

B

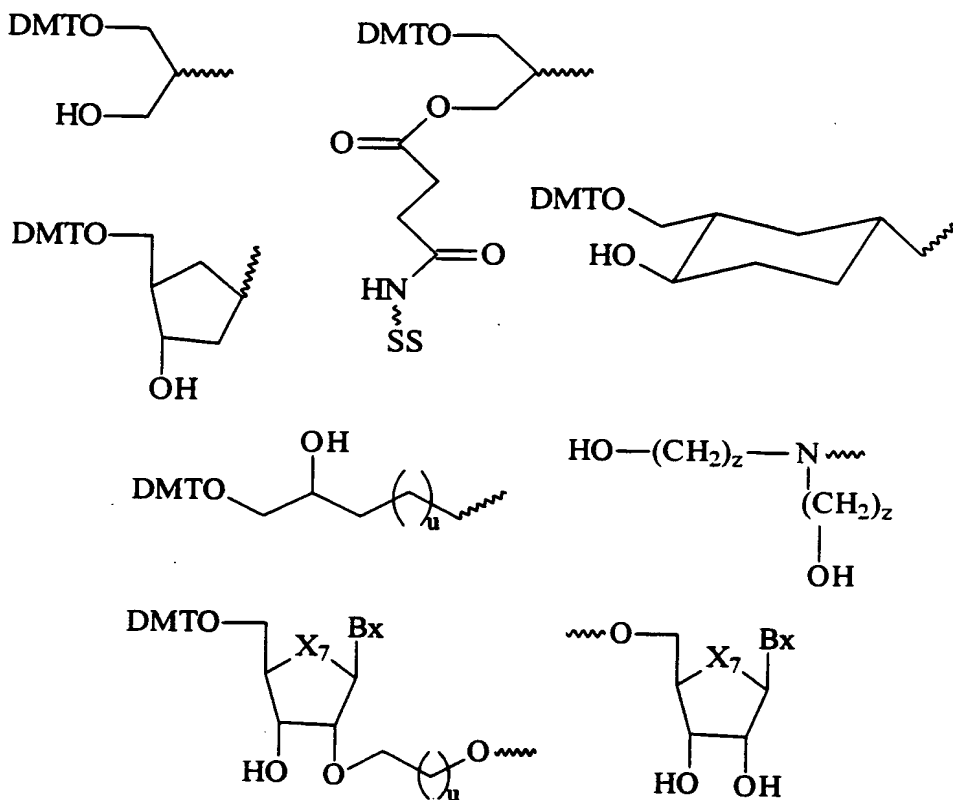
8. The compound of claim <sup>101</sup> ~~7~~ wherein said amino acid is amino caproic acid.

B

9. The compound of claim <sup>101</sup> ~~7~~ wherein said X<sub>4</sub> is the side  
20 chain of glutamic acid.

B

10. The compound of claim <sup>101</sup> ~~7~~ wherein said X<sub>6</sub> has one of  
the formulas:



wherein

5

SS is a solid support;

$X_7$  is O or  $CH_2$ ;

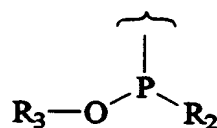
Bx is a nucleobase,  $C_4$ - $C_{14}$  heterocyclyl or hydrogen;

z is an integer from 1 to 50; and

u is an integer from 2 to 5.

11. The compound of claim <sup>10</sup> wherein said  $R_1$  is dimethoxytrityl.

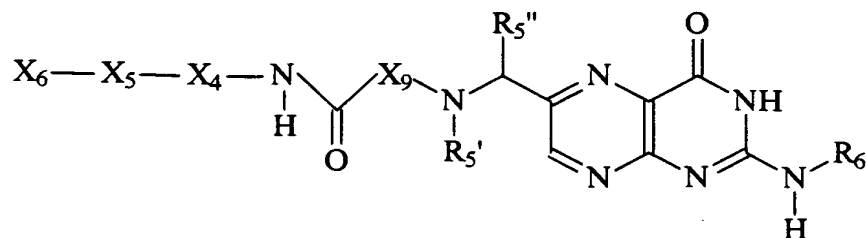
12. The compound of claim <sup>10</sup> wherein said  $R_{20}$  is a group of formula:





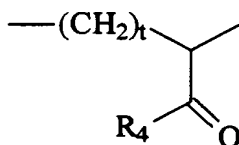
wherein  $R_2$  is diisopropylamino and  $R_3$  is  $\beta$ -cyanoethyl.

13. A compound of the formula:



wherein:

$X_4$  is  $-\text{CH}(X_4)$  or a group of formula:



5

$X_4$  is the side chain of a naturally-occurring or non-naturally-occurring amino acid, or a protected side chain of a naturally-occurring or non-naturally-occurring amino acid;

$X_5$  is  $-\text{N}(X_6)\text{C}(\text{O})-$ ,  $-\text{C}(\text{O})\text{NH}-$ ,  $-\text{NHC}(\text{O})-$ ,  $-\text{OC}(\text{O})\text{NH}-$ ,  
 10  $-\text{C}(\text{S})\text{NH}-$ ,  $-\text{SC}(\text{S})\text{NH}-$ ,  $-\text{SC}(\text{O})\text{NH}-$ ,  $-\text{OC}(\text{S})\text{NH}-$ ,  $-\text{C}(\text{O})\text{O}-$ ,  
 $-\text{C}(\text{O})(\text{CH}_2)_n-$  or a bond;

$n$  is an integer from 1 to 50;

each  $X_6$ ,  $X_6$ , and  $X_9$  is, independently, a bond, hydrogen or  
 a hydrocarbyl group selected from  $\text{C}_1$ - $\text{C}_{10}$  alkyl,  $\text{C}_2$ - $\text{C}_{10}$  alkenyl,  
 15  $\text{C}_2$ - $\text{C}_{20}$  alkynyl,  $\text{C}_6$ - $\text{C}_{14}$  aryl,  $\text{C}_6$ - $\text{C}_{14}$  aralkyl,  $\text{C}_3$ - $\text{C}_{14}$  cycloalkyl,  
 $\text{C}_5$ - $\text{C}_{14}$  fused cycloalkyl,  $\text{C}_4$ - $\text{C}_{14}$  heterocycle,  $\text{C}_4$ - $\text{C}_{14}$   
 heterocyclalkyl,  $\text{C}_4$ - $\text{C}_{14}$  heteroaryl and  $\text{C}_4$ - $\text{C}_{14}$  heteroarylalkyl;  
 wherein said hydrocarbyl group is substituted with at least  
 two hydroxyl groups, and is optionally substituted with oxo,  
 20 acyl, alkoxy, alkoxy carbonyl, alkyl, alkenyl, alkynyl, amino,  
 amido, azido, aryl, heteroaryl, carboxylic acid, cyano,  
 guanidino, halo, haloalkyl, haloalkoxy, hydrazino, ODMT,  
 alkylsulfonyl, nitro, sulfide, disulfide, sulfone, sulfonate,

sulfonamide, thiol, and thioalkoxy; provided that each of  $X_6$  and  $X_6$  is not a bond and  $X_6$  is not hydrogen;

$R_4$  is a hydroxyl group or a protected hydroxyl group;

$R_5$  is hydrogen,  $C_1$ - $C_{10}$  alkyl,  $C_2$ - $C_{10}$  alkenyl,  $C_2$ - $C_{20}$  alkynyl,  $C_6$ - $C_{14}$  aryl or an amino-protecting group

$R_5$  is hydrogen,  $C_1$ - $C_{10}$  alkyl,  $C_2$ - $C_{10}$  alkenyl,  $C_2$ - $C_{20}$  alkynyl,  $C_6$ - $C_{14}$  aryl,  $C_6$ - $C_{14}$  aralkyl,  $C_3$ - $C_{14}$  cycloalkyl, formyl, aminoalkyl or hydroxymethyl;

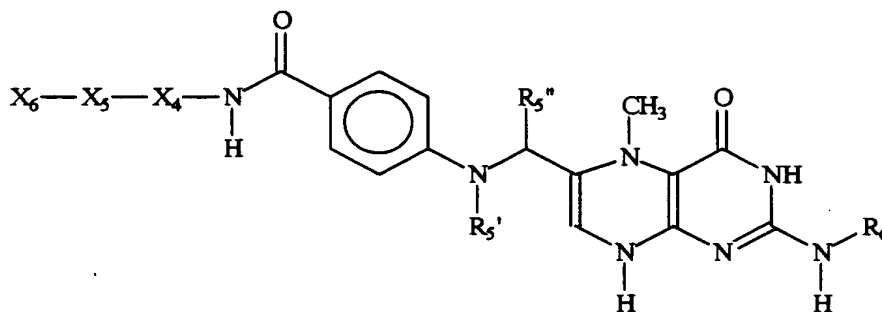
$R_6$  is hydrogen or an amino protecting group; and

$t$  is 1 or 2.

14. The compound of claim 13 wherein said amino acid is aminocaproic acid

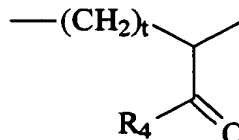
15. The compound of claim 13 connected to an oligonucleotide by a disulfide group.

16. A compound of the formula:



wherein:

$X_4$  is  $-CH(X_4)$  or a group of formula:



$X_4$  is the side chain of a naturally-occurring or non-naturally-occurring amino acid, or a protected side chain of a naturally-occurring or non-naturally-occurring amino acid;

$X_5$  is  $-N(X_6)C(O)-$ ,  $-C(O)NH-$ ,  $-NHC(O)-$ ,  $-OC(O)NH-$ ,  
 $-C(S)NH-$ ,  $-SC(S)NH-$ ,  $-SC(O)NH-$ ,  $-OC(S)NH-$ ,  $-C(O)O-$ ,  
 $-C(O)(CH_2)_n-$  or a bond;

$n$  is an integer from 1 to 50;

- 5 each  $X_6$  and  $X_6$  is, independently, hydrogen or a hydrocarbyl group selected from  $C_1$ - $C_{10}$  alkyl,  $C_2$ - $C_{10}$  alkenyl,  $C_2$ - $C_{20}$  alkynyl,  $C_6$ - $C_{14}$  aryl,  $C_6$ - $C_{14}$  aralkyl,  $C_3$ - $C_{14}$  cycloalkyl,  $C_5$ - $C_{14}$  fused cycloalkyl,  $C_4$ - $C_{14}$  heterocycle,  $C_4$ - $C_{14}$  heterocyclalkyl,  $C_4$ - $C_{14}$  heteroaryl and  $C_4$ - $C_{14}$  heteroarylalkyl;
- 10 wherein said hydrocarbyl group is substituted with at least two hydroxyl groups, and optionally substituted with oxo, acyl, alkoxy, alkoxycarbonyl, alkyl, alkenyl, alkynyl, amino, amido, azido, aryl, heteroaryl, carboxylic acid, cyano, guanidino, halo, haloalkyl, haloalkoxy, hydrazino, ODMT,
- 15 alkylsulfonyl, nitro, sulfide, disulfide, sulfone, sulfonate, sulfonamide, thiol, and thioalkoxy; provided that  $X_6$  is not hydrogen;

$R_4$  is a hydroxyl group or a protected hydroxyl group;

- $R_5$  is hydrogen,  $C_1$ - $C_{10}$  alkyl,  $C_2$ - $C_{10}$  alkenyl,  $C_2$ - $C_{20}$  alkynyl,  $C_6$ - $C_{14}$  aryl or an amino-protecting group
- 20  $R_5$  is hydrogen,  $C_1$ - $C_{10}$  alkyl,  $C_2$ - $C_{10}$  alkenyl,  $C_2$ - $C_{20}$  alkynyl,  $C_6$ - $C_{14}$  aryl,  $C_6$ - $C_{14}$  aralkyl,  $C_3$ - $C_{14}$  cycloalkyl, formyl, aminoalkyl or hydroxymethyl;

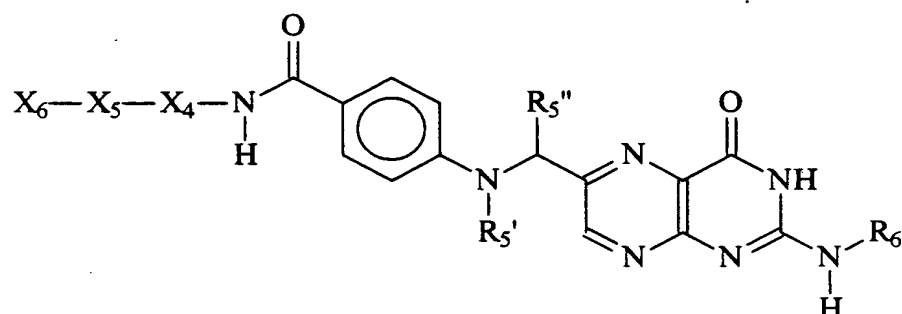
$R_6$  is hydrogen or an amino protecting group; and

- 25  $t$  is 1 or 2.

17. The compound of claim 16 wherein said amino acid is aminocaproic acid.

18. The compound of claim 16 connected to an oligonucleotide by a disulfide group.

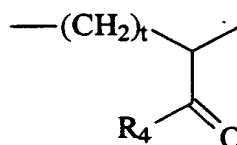
- 30 19. A method of preparing compounds of formula XVII:



XVII

wherein:

$X_4$  is  $-\text{CH}(X_4')$  or a group of formula:



5

$X_4'$  is the side chain of a naturally-occurring or non-naturally-occurring amino acid, or a protected side chain of a naturally-occurring or non-naturally-occurring amino acid;

$X_5$  is  $-\text{N}(X_6')\text{C}(=\text{O})-$ ,  $-\text{C}(=\text{O})\text{NH}-$ ,  $-\text{NHC}(=\text{O})-$ ,  $-\text{OC}(=\text{O})\text{NH}-$ ,  
 10  $-\text{C}(=\text{S})\text{NH}-$ ,  $-\text{SC}(=\text{S})\text{NH}-$ ,  $-\text{SC}(=\text{O})\text{NH}-$ ,  $-\text{OC}(=\text{S})\text{NH}-$ ,  $-\text{C}(=\text{O})\text{O}-$ ,  
 $-\text{C}(=\text{O})(\text{CH}_2)_n-$  or a bond;

$n$  is an integer from 1 to 50;

each  $X_6'$  and  $X_6$  is, independently, hydrogen or a hydrocarbyl group selected from  $\text{C}_1$ - $\text{C}_{10}$  alkyl,  $\text{C}_2$ - $\text{C}_{10}$  alkenyl,  
 15  $\text{C}_2$ - $\text{C}_{20}$  alkynyl,  $\text{C}_6$ - $\text{C}_{14}$  aryl,  $\text{C}_6$ - $\text{C}_{14}$  aralkyl,  $\text{C}_3$ - $\text{C}_{14}$  cycloalkyl,  $\text{C}_5$ - $\text{C}_{14}$  fused cycloalkyl,  $\text{C}_4$ - $\text{C}_{14}$  heterocycle,  $\text{C}_4$ - $\text{C}_{14}$  heterocyclalkyl,  $\text{C}_4$ - $\text{C}_{14}$  heteroaryl and  $\text{C}_4$ - $\text{C}_{14}$  heteroarylalkyl;  
 wherein said hydrocarbyl group is substituted with at least two hydroxyl groups, and is optionally substituted with oxo,  
 20 acyl, alkoxy, alkoxycarbonyl, alkyl, alkenyl, alkynyl, amino, amido, azido, aryl, heteroaryl, carboxylic acid, cyano, guanidino, halo, haloalkyl, haloalkoxy, hydrazino, ODMT, alkylsulfonyl, nitro, sulfide, disulfide, sulfone, sulfonate,

sulfonamide, thiol, and thioalkoxy; provided that  $X_6$  is not hydrogen;

$R_4$  is a hydroxyl group or a protected hydroxyl group;

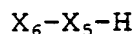
$R_5$  is hydrogen,  $C_1$ - $C_{10}$  alkyl,  $C_2$ - $C_{10}$  alkenyl,  $C_2$ - $C_{20}$  alkynyl,  $C_6$ - $C_{14}$  aryl or an amino-protecting group

$R_{5'}$  is hydrogen,  $C_1$ - $C_{10}$  alkyl,  $C_2$ - $C_{10}$  alkenyl,  $C_2$ - $C_{20}$  alkynyl,  $C_6$ - $C_{14}$  aryl,  $C_6$ - $C_{14}$  aralkyl,  $C_3$ - $C_{14}$  cycloalkyl, formyl, aminoalkyl or hydroxymethyl;

$R_6$  is hydrogen or an amino protecting group; and  
10  $t$  is 1 or 2;

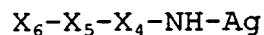
comprising the steps of:

(a) providing a hydroxy compound of formula:



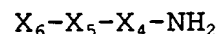
(b) protecting said hydroxyl groups of  $X_6$  with protecting  
15 groups to form a protected hydroxy compound;

(c) reacting said protected hydroxy compound with an amino-protected amino acid to form a covalently linked hydroxy compound of formula:



20 wherein  $Ag$  is an amino protecting group;

(d) cleaving the amino-protecting group of said covalently linked hydroxy compound to form a hydroxy compound bearing a deprotected amino group and having formula:



25 (e) reacting said amino group with a folate moiety; and

(f) cleaving the protecting groups on said hydroxyl groups of step (b) to form a compound of formula XVII.

20. The method of claim 19 further comprising the steps of:

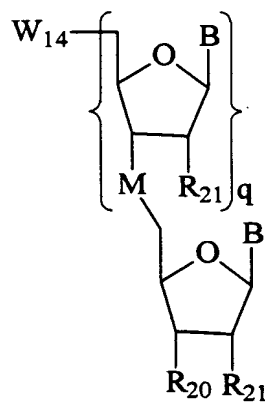
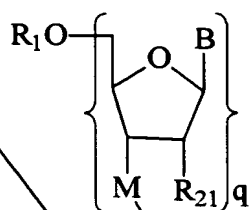
30 (g) protecting one of said hydroxyl groups of  $X_6$  with a dimethoxytrityl group; and

(h) phosphitylating the other of said hydroxyl groups of

1000000-1000000

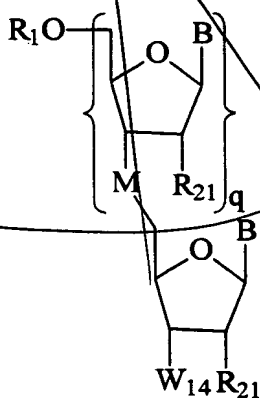
$X_6$ .

21. A compound having formula XVIA, XVIB, XVIC or XVID:

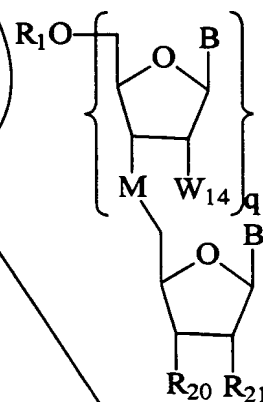


XVIA

XVIC



XVIB

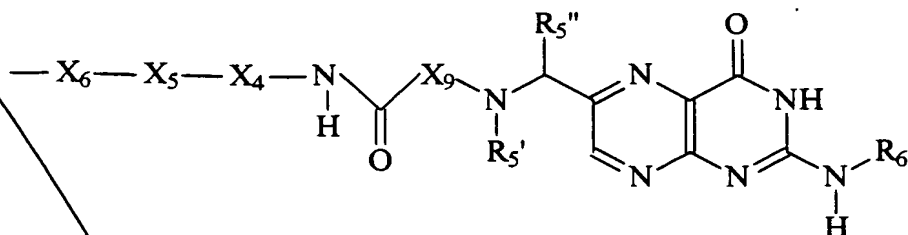


XVID

5

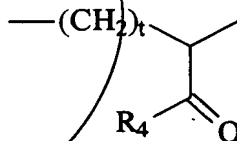
wherein:

$W_{14}$  has the formula:



wherein:

X<sub>4</sub> is -CH(X<sub>4</sub>) or a group of formula:



X<sub>4</sub> is the side chain of a naturally-occurring or non-naturally-occurring amino acid, or a protected side chain of a naturally-occurring or non-naturally-occurring amino acid;

t is 1 or 2;

X<sub>5</sub> is -N(X<sub>6</sub>)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-,  
-C(S)NH-, -SC(S)NH-, -SC(O)NH-, -OC(S)NH-, -C(O)O-,  
-C(O)(CH<sub>2</sub>)<sub>n</sub>- or a bond;

n is an integer from 1 to 50;

each X<sub>6</sub>, X<sub>6</sub>, and X<sub>9</sub> is, independently, a bond, hydrogen or a hydrocarbyl group selected from C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl, C<sub>2</sub>-C<sub>20</sub> alkynyl, C<sub>6</sub>-C<sub>14</sub> aryl, C<sub>6</sub>-C<sub>14</sub> aralkyl, C<sub>3</sub>-C<sub>14</sub> cycloalkyl, C<sub>5</sub>-C<sub>14</sub> fused cycloalkyl, C<sub>4</sub>-C<sub>14</sub> heterocycle, C<sub>4</sub>-C<sub>14</sub> heterocyclalkyl, C<sub>4</sub>-C<sub>14</sub> heteroaryl and C<sub>4</sub>-C<sub>14</sub> heteroarylalkyl;

wherein said hydrocarbyl group is substituted with at least two hydroxyl groups, and is optionally substituted with oxo, acyl, alkoxy, alkoxycarbonyl, alkyl, alkenyl, alkynyl, amino, amido, azido, aryl, heteroaryl, carboxylic acid, cyano, guanidino, halo, haloalkyl, haloalkoxy, hydrazino, ODMT, alkylsulfonyl, nitro, sulfide, disulfide, sulfone, sulfonate,

00973991-100001

sulfonamide, thiol, and thioalkoxy; provided that each  $X_6$  and  $X_9$  is not hydrogen and  $X_6$  is not a bond;

$R_1$  is hydrogen or a hydroxyl protecting group;

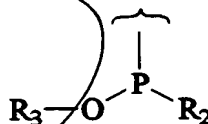
$R_4$  is a hydroxyl group or a protected hydroxyl group;

5 each  $R_5$  and  $R_{10}$  is, independently, hydrogen,  $C_1$ - $C_{10}$  alkyl,  $C_2$ - $C_{10}$  alkenyl,  $C_2$ - $C_{20}$  alkynyl,  $C_6$ - $C_{14}$  aryl or an amino-protecting group

$R_{5'}$  is hydrogen,  $C_1$ - $C_{10}$  alkyl,  $C_2$ - $C_{10}$  alkenyl,  $C_2$ - $C_{20}$  alkynyl,  $C_6$ - $C_{14}$  aryl,  $C_6$ - $C_{14}$  aralkyl,  $C_3$ - $C_{14}$  cycloalkyl, formyl, 10 aminoalkyl or hydroxymethyl;

$R_6$  is hydrogen or an amino protecting group;

$R_{20}$  is hydrogen or a group of formula:



$R_2$  is  $-N(R_7)_2$ , or a heterocycloalkyl or 15 heterocycloalkenyl ring containing from 4 to 7 atoms, and having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;

$R_7$  is straight or branched chain alkyl having from 1 to 10 carbons;

20  $R_3$  is a phosphorus protecting group;

$R_{21}$  is hydrogen, hydroxyl, fluoro or a group of formula  $Z-R_{22}-(R_{23})_v$ ;

$Z$  is O, S, NH or  $N-R_{22}-(R_{23})_v$ ;

$R_{22}$  is  $C_1$ - $C_{20}$  alkyl,  $C_2$ - $C_{20}$  alkenyl, or  $C_2$ - $C_{20}$  alkynyl;

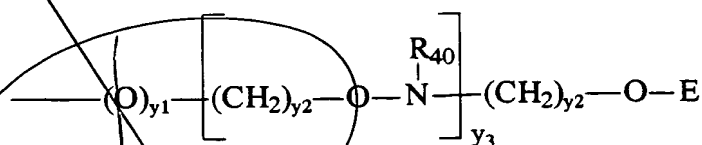
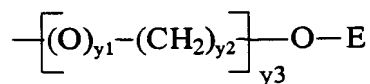
25  $R_{23}$  is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, 30 hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide,

"106600" 106600



polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

5 or R<sub>21</sub> has one of the formulas:



wherein:

y<sub>1</sub> is 0 or 1;

each y<sub>2</sub> is, independently, 0 to 10;

10 y<sub>3</sub> is 1 to 10;

E is N(R<sub>41</sub>)(R<sub>42</sub>) or N=C(R<sub>41</sub>)(R<sub>42</sub>);

15 each R<sub>41</sub> and each R<sub>42</sub> is independently H, C<sub>1</sub>-C<sub>10</sub> alkyl, a nitrogen protecting group, or R<sub>41</sub> and R<sub>42</sub> taken together form a nitrogen protecting group; or R<sub>41</sub> and R<sub>42</sub> taken together with the N or C atom to which they are attached form a ring structure that can include at least one heterotom selected from N and O;

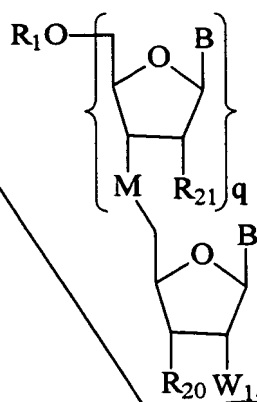
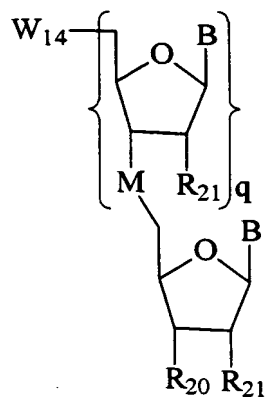
B is a nucleobase;

M is an optionally protected internucleoside linkage;

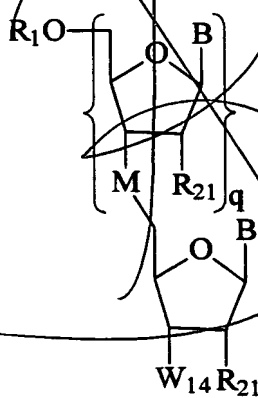
20 q is from zero to about 50; and

v is from zero to about 10.

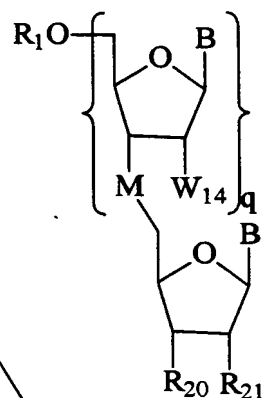
22. A compound having formula XVIA, XVIB, XVIC or XVID:

~~XVIA~~

XVIC



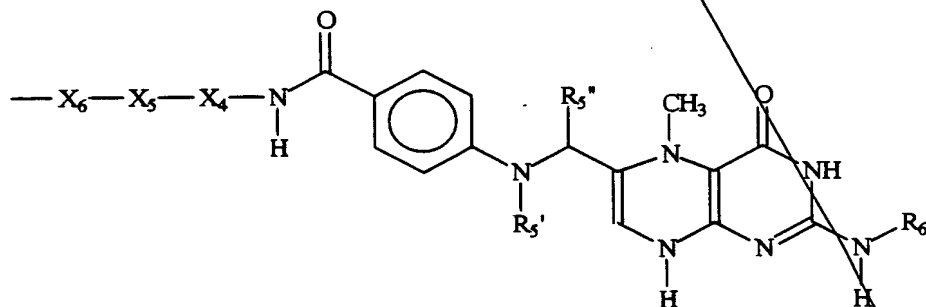
XVIB



XVID

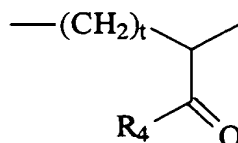
wherein:

$W_{14}$  has the formula:



wherein:

$X_4$  is  $-\text{CH}(X_4)$  or a group of formula:



$X_4$  is the side chain of a naturally-occurring or non-naturally-occurring amino acid, or a protected side chain of a naturally-occurring or non-naturally-occurring amino acid;

$t$  is 1 or 2;

$X_5$  is  $-\text{N}(X_6)\text{C}(\text{O})-$ ,  $-\text{C}(\text{O})\text{NH}-$ ,  $-\text{NHC}(\text{O})-$ ,  $-\text{OC}(\text{O})\text{NH}-$ ,  $-\text{C}(\text{S})\text{NH}-$ ,  $-\text{SC}(\text{S})\text{NH}-$ ,  $-\text{SC}(\text{O})\text{NH}-$ ,  $-\text{OC}(\text{S})\text{NH}-$ ,  $-\text{C}(\text{O})\text{O}-$ ,  $-\text{C}(\text{O})(\text{CH}_2)_n-$  or a bond;

$n$  is an integer from 1 to 50;

each  $X_6$  and  $X_6$  is, independently, a bond, hydrogen or a hydrocarbyl group selected from  $\text{C}_1\text{-C}_{10}$  alkyl,  $\text{C}_2\text{-C}_{10}$  alkenyl,  $\text{C}_2\text{-C}_{20}$  alkynyl,  $\text{C}_6\text{-C}_{14}$  aryl,  $\text{C}_6\text{-C}_{14}$  aralkyl,  $\text{C}_3\text{-C}_{14}$  cycloalkyl,  $\text{C}_5\text{-C}_{14}$  fused cycloalkyl,  $\text{C}_4\text{-C}_{14}$  heterocycle,  $\text{C}_4\text{-C}_{14}$  heterocyclalkyl,  $\text{C}_4\text{-C}_{14}$  heteroaryl and  $\text{C}_4\text{-C}_{14}$  heteroarylalkyl; wherein said hydrocarbyl group is substituted with at least two hydroxyl groups, and is optionally substituted with oxo, acyl, alkoxy, alkoxycarbonyl, alkyl, alkenyl, alkynyl, amino, amido, azido, aryl, heteroaryl, carboxylic acid, cyano, guanidino, halo, haloalkyl, haloalkoxy, hydrazino, ODMT, alkylsulfonyl, nitro, sulfide, disulfide, sulfone, sulfonate, sulfonamide, thiol, and thioalkoxy; provided that  $X_6$  is not hydrogen and  $X_6$  is not a bond;

$R_1$  is hydrogen or a hydroxyl protecting group;

$R_4$  is a hydroxyl group or a protected hydroxyl group;

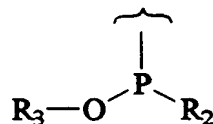
each  $R_5$  and  $R_{40}$  is, independently, hydrogen,  $\text{C}_1\text{-C}_{10}$  alkyl,  $\text{C}_2\text{-C}_{10}$  alkenyl,  $\text{C}_2\text{-C}_{20}$  alkynyl,  $\text{C}_6\text{-C}_{14}$  aryl or an amino-protecting group

$R_{5..}$  is hydrogen,  $\text{C}_1\text{-C}_{10}$  alkyl,  $\text{C}_2\text{-C}_{10}$  alkenyl,  $\text{C}_2\text{-C}_{20}$  alkynyl,  $\text{C}_6\text{-C}_{14}$  aryl,  $\text{C}_6\text{-C}_{14}$  aralkyl,  $\text{C}_3\text{-C}_{14}$  cycloalkyl, formyl,

aminoalkyl or hydroxymethyl;

$R_6$  is hydrogen or an amino protecting group;

$R_{20}$  is hydrogen or a group of formula:



5  $R_2$  is  $-N(R_7)_2$ , or a heterocycloalkyl or heterocycloalkenyl ring containing from 4 to 7 atoms, and having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;

10  $R_7$  is straight or branched chain alkyl having from 1 to 10 carbons;

$R_3$  is a phosphorus protecting group;

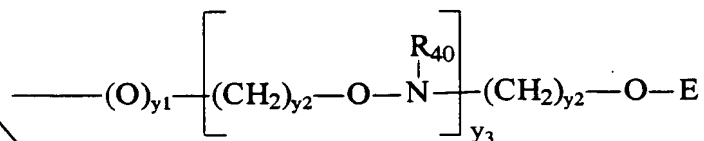
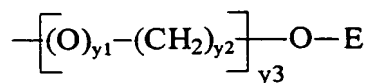
$R_{21}$  is hydrogen, hydroxyl, fluoro or a group of formula  $Z-R_{22}-(R_{23})_v$ ;

$Z$  is O, S, NH or  $N-R_{22}-(R_{23})_v$ ;

15  $R_{22}$  is  $C_1-C_{20}$  alkyl,  $C_2-C_{20}$  alkenyl, or  $C_2-C_{20}$  alkynyl;

20  $R_{23}$  is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the  
25 pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

or  $R_{21}$  has one of the formulas:



wherein:

y<sub>1</sub> is 0 or 1;

each y<sub>2</sub> is, independently, 0 to 10;

5 y<sub>3</sub> is 1 to 10;

E is N(R<sub>41</sub>)(R<sub>42</sub>) or N=C(R<sub>41</sub>)(R<sub>42</sub>);

each R<sub>41</sub> and each R<sub>42</sub> is independently H, C<sub>1</sub>-C<sub>10</sub> alkyl, a  
nitrogen protecting group, or R<sub>41</sub> and R<sub>42</sub> taken together form a  
nitrogen protecting group, or R<sub>41</sub> and R<sub>42</sub> taken together with  
10 the N or C atom to which they are attached form a ring  
structure that can include at least one heterotom selected  
from N and O;

B is a nucleobase;

M is an optionally protected internucleoside linkage;

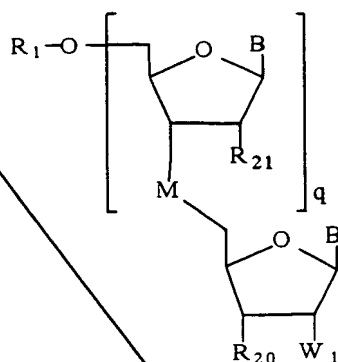
15 q is from zero to about 50; and

v is from zero to about 10.

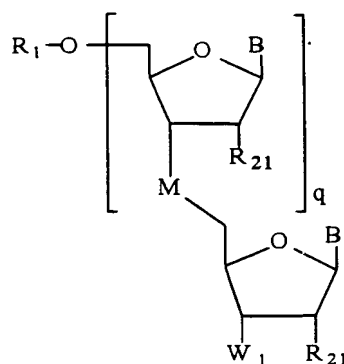
23. A synthetic method comprising the steps of:

(a) providing a compound of formula IA, IB, IC or ID:

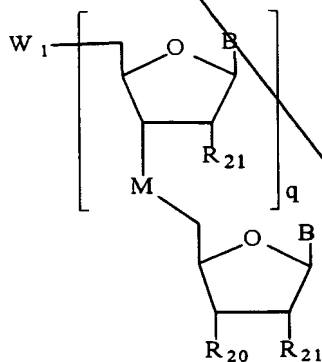
T0600T T0600T



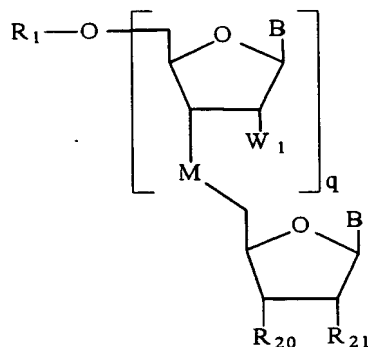
IA



IB



IC



ID

wherein:

$W_1$  is a linking group, O, NH, or S;

$R_1$  is H or a hydroxyl protecting group;

5 B is a nucleobase;

each  $R_{21}$  is H, OH, F, or a group of formula  $Z-R_{22}-(R_{23})_v$ ;

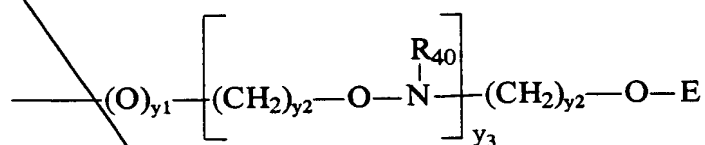
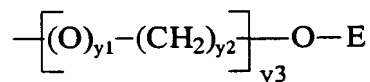
Z is O, S, NH, or  $N-R_{22}-(R_{23})_v$

$R_{22}$  is  $C_1-C_{20}$  alkyl,  $C_2-C_{20}$  alkenyl, or  $C_2-C_{20}$  alkynyl;

10  $R_{23}$  is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, 15 disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide,

polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

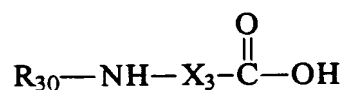
- 5           v is from 0 to about 10;  
or R<sub>21</sub> has one of the formulas:



wherein:

- 10           y<sub>1</sub> is 0 or 1;  
            y<sub>2</sub> is 0 to 10;  
            y<sub>3</sub> is 1 to 10;  
            E is N(R<sub>41</sub>)(R<sub>42</sub>) or N=C(R<sub>41</sub>)(R<sub>42</sub>);  
            each R<sub>41</sub> and each R<sub>42</sub> is independently H, C<sub>1</sub>-C<sub>10</sub> alkyl, a nitrogen protecting group, or R<sub>41</sub> and R<sub>42</sub> taken together form a nitrogen protecting group; or R<sub>41</sub> and R<sub>42</sub> taken together with the N or C atom to which they are attached form a ring structure that can include at least one heterotom selected from N and O;  
20           q is from 0 to about 50;  
            M is an optionally protected internucleoside linkage;

(b) reacting said compound of formula I with a compound of formula II:

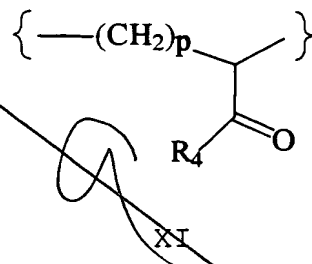


II

wherein:

~~R<sub>30</sub>~~ is an amino protecting group;

~~X<sub>3</sub> is -CH(Z<sub>1</sub>)-~~ or a group of Formula XI:

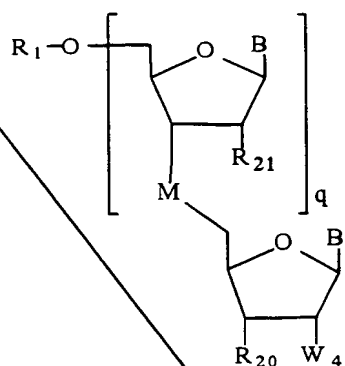


~~Z<sub>1</sub> is the sidechain of a naturally occurring amino acid,  
or a protected sidechain of a naturally occurring amino acid;~~

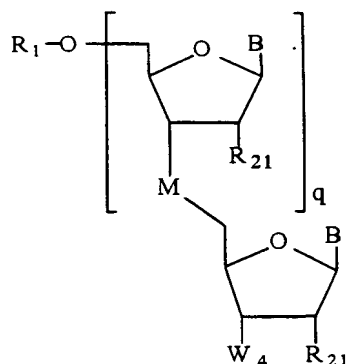
p is 1 or 2;

10 to form a compound of formula IVA, IVB, ~~IVC~~, or IVD:

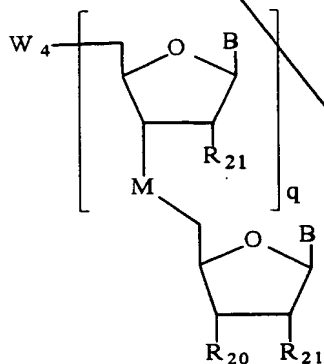




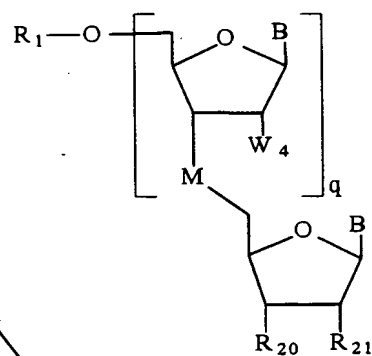
IV A



IV B



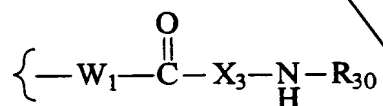
IV C



IV D

wherein:

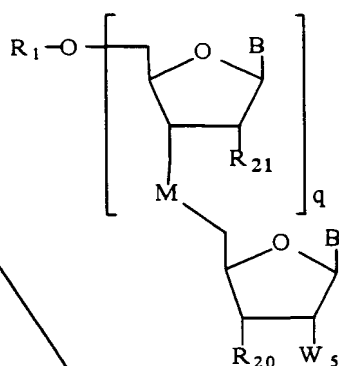
$\text{W}_4$  has the formula:



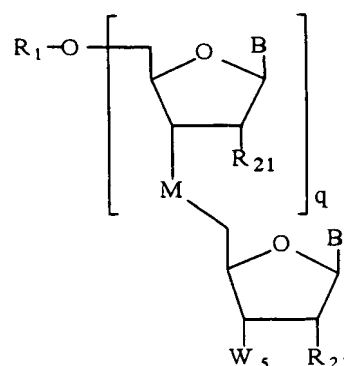
5

and

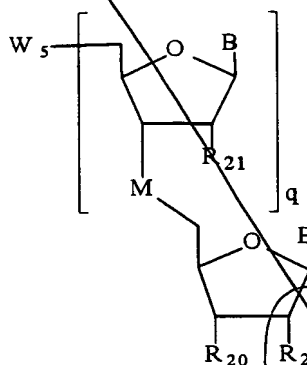
treating said compound of formula IV A, IV B, IV C or IV D with a deprotecting reagent to form a compound of formula VA, VB, VC or VD:



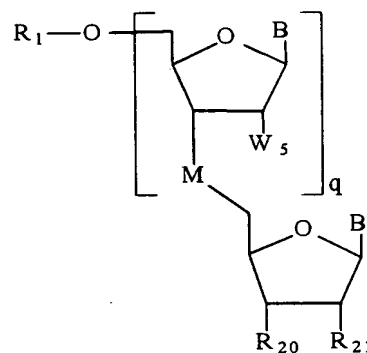
VA



VB

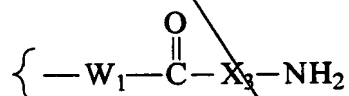


VC

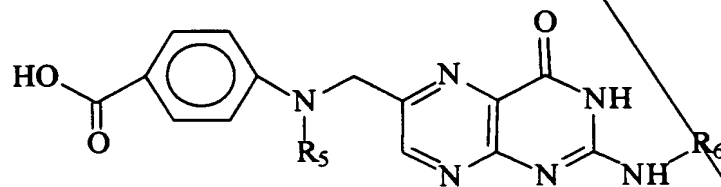


VD

wherein  $W_5$  has the formula:



24. The method of claim 23 further comprising  
5 condensing said compound of formula V with a compound of  
formula VI:

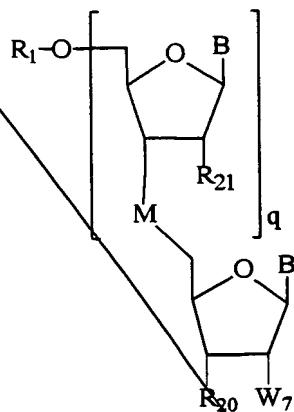


VI

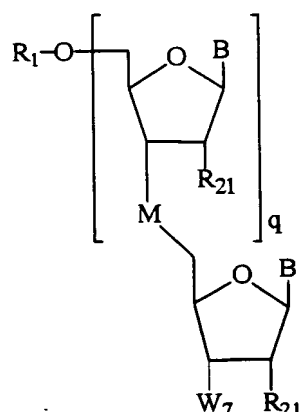
$R_5$  is H or an amino protecting group;

$R_6$  is H or an amino protecting group;

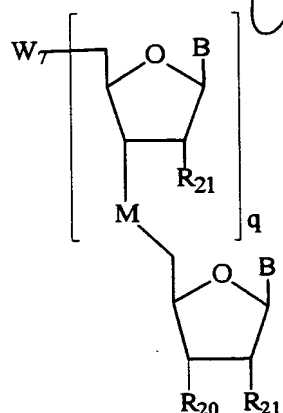
to form a compound of formula VIIA, VIIB, VIIC, or VIID:



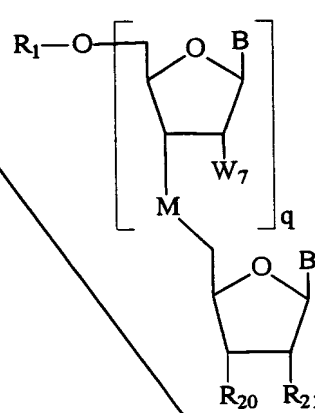
VIIA



VIIB

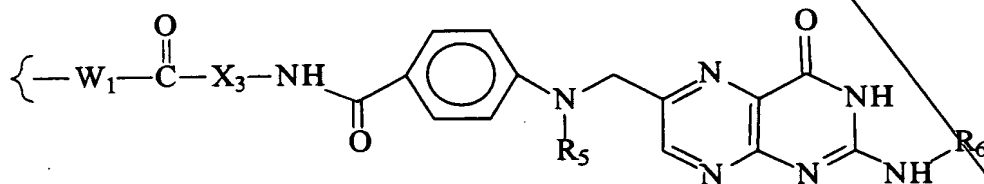


VIIC

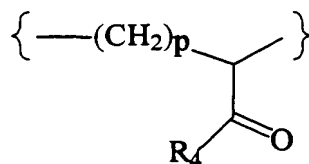


VIID

5 wherein  $W_7$  has the formula:



25. The method of claim 24 wherein  $X_3$  is a group of formula XI:



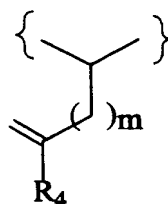
XI

5 wherein:

$p$  is 1 or 2;

$R_4$  is a hydroxyl group, or a protected hydroxy group;

or  $X_3$  is a group of formula XII:



XII

10

wherein  $m$  is 1 or 2.

26. The method of claim 25 wherein  $q$  is 0.

27. The method of claim 25 wherein  $R_{30}$  is fluorene-9-yl methoxycarbonyl.

15 28. The method of claim 25 wherein  $X_3$  is a group of formula XI.

29. The method of claim 25 wherein  $W_1$  has the formula  $\text{---O---}(\text{CH}_2)_n\text{---NH---}$ , wherein  $n$  is from 1 to about 10.

30. The method of claim 29 wherein  $n$  is 6.

20 31. The method of claim 25 wherein  $X_3$  is a group of formula XII.

T06007" T0602600

B

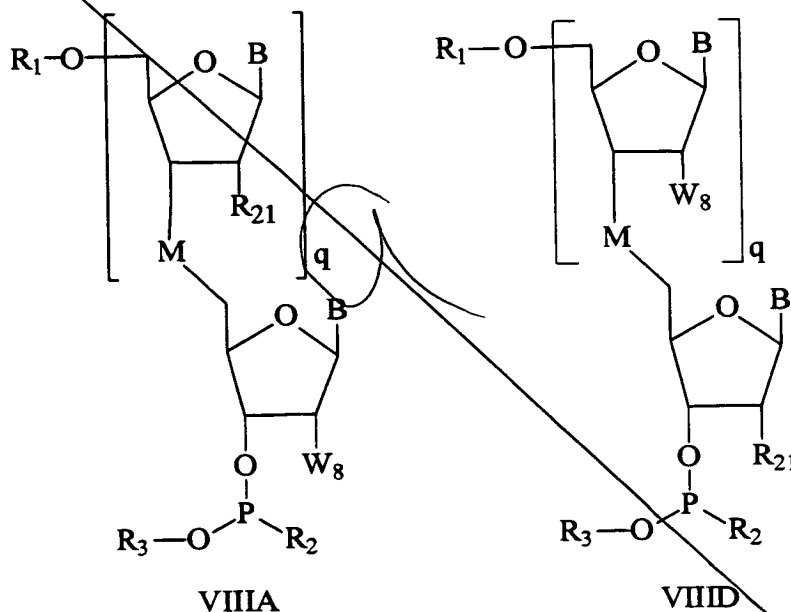
32. The method of claim <sup>104</sup>31 wherein  $W_1$  has the formula  $-O-(CH_2)_n-NH-$ , wherein  $n$  is from 1 to about 10.

33. The method of claim 32 wherein  $n$  is 6.

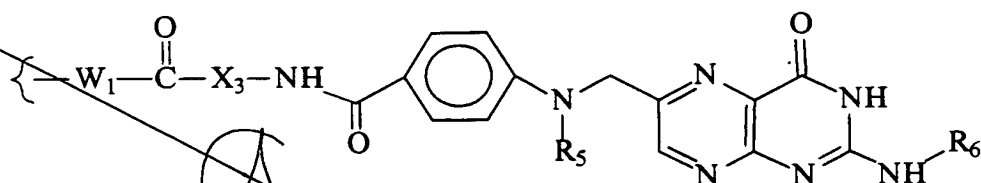
34. The method of claim 28 wherein  $R_1$  is 5 dimethoxytrityl,  $W_1$  has the formula  $-O-(CH_2)_n-NH-$  where  $n$  is 6,  $p$  is 2,  $R_4$  is *t*-butoxy,  $R_5$  is trifluoroacetyl,  $R_6$  is  $-C(=O)-CH(CH_3)_2$ , and  $R_{30}$  is FMOC.

Sub 134 35. The method of claim 31 wherein  $R_1$  is dimethoxytrityl,  $A$  has the formula  $-O-(CH_2)_n-NH-$  where  $n$  is 6,  $m$  is 2,  $R_4$  is *t*-butoxy,  $R_5$  is trifluoroacetyl,  $R_6$  is  $-C(=O)-CH(CH_3)_2$ , and  $R_{30}$  is FMOC.

36. The method of claim 24 further comprising contacting said compound of formula VIIA or VIID with a phosphitylating reagent to form a compound of formula VIIIA or VIIIAD:



wherein  $W_7$  has the formula:



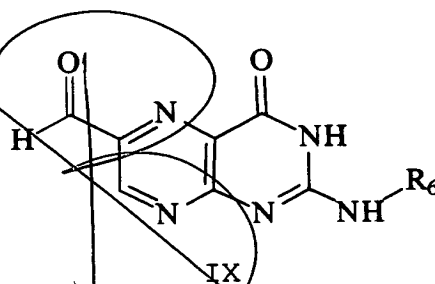
37. The method of claim 36 wherein  $X_3$  has the formula XI.

5 38. The method of claim 36 wherein  $X_3$  has the formula XII.

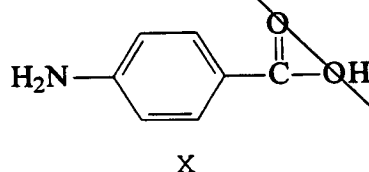
39. The method of claim 37 wherein  $R_1$  is dimethoxytrityl,  $W_1$  has the formula  $-\text{O}-(\text{CH}_2)_n-\text{NH}-$  where  $n$  is 6,  $p$  is 2,  $R_4$  is *t*-butoxy,  $R_5$  is trifluoroacetyl,  $R_6$  is -  
10  $\text{C}(=\text{O})-\text{CH}(\text{CH}_3)_2$ , and  $R_{30}$  is Fmoc.

Sub 35 40. The method of claim 38 wherein  $R_1$  is dimethoxytrityl,  $W_1$  has the formula  $-\text{O}-(\text{CH}_2)_n-\text{NH}-$  where  $n$  is 6,  $m$  is 2,  $R_4$  is *t*-butoxy,  $R_5$  is trifluoroacetyl,  $R_6$  is -  
 $\text{C}(=\text{O})-\text{CH}(\text{CH}_3)_2$ , and  $R_{30}$  is Fmoc.

15 41. The method of claim 25 wherein said compound of formula VI is prepared by the steps of reacting a compound of formula IX:

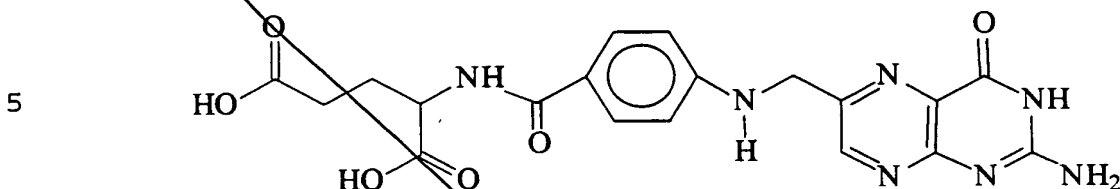


20 with a compound of formula X:

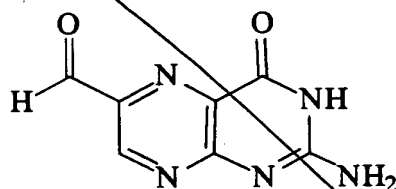


and treating the product of said reaction with a protecting group reagent to form said compound of formula VI.

42. The method of claim 26 wherein said compound IX is prepared by reacting folic acid:



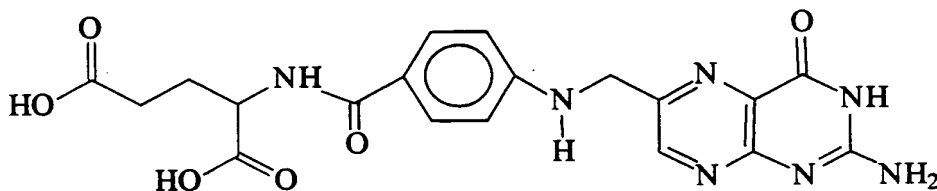
with a reagent effective to form pterin aldehyde:



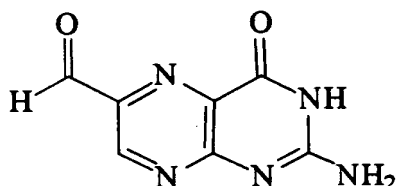
and

protecting the amino group of said pterin aldehyde.

10        43.    A method for the preparation of a folic acid  
derivative comprising the steps of reacting folic acid:



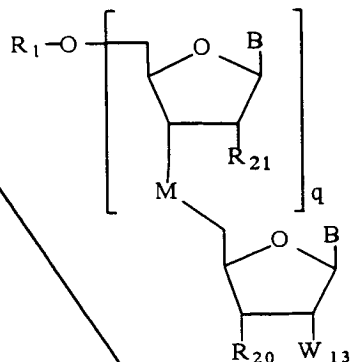
with a reagent effective to form pterin aldehyde:



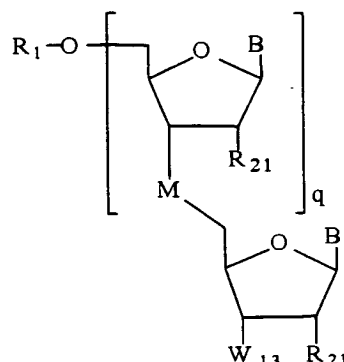
15        44.    The method of claim 43 further comprising  
protecting the amino group of said pterin aldehyde.

Variable	Mean	Standard deviation	Minimum	Maximum
Age	34.5	10.5	20	55
Gender	0.5	0.5	0	1
Marital status	0.5	0.5	0	1
Education	12.5	2.5	9	16
Income	1.5	0.5	1	2
Health	0.5	0.5	0	1
Smoking	0.5	0.5	0	1
Alcohol	0.5	0.5	0	1
Exercise	0.5	0.5	0	1
Stress	0.5	0.5	0	1
Sleep	0.5	0.5	0	1
Appetite	0.5	0.5	0	1
Mood	0.5	0.5	0	1
Energy	0.5	0.5	0	1
Concentration	0.5	0.5	0	1
Memory	0.5	0.5	0	1
Emotion	0.5	0.5	0	1
Behavior	0.5	0.5	0	1
Thought	0.5	0.5	0	1
Feeling	0.5	0.5	0	1
Perception	0.5	0.5	0	1
Attention	0.5	0.5	0	1
Intuition	0.5	0.5	0	1
Imagination	0.5	0.5	0	1
Reasoning	0.5	0.5	0	1
Logic	0.5	0.5	0	1
Analysis	0.5	0.5	0	1
Synthesis	0.5	0.5	0	1
Evaluation	0.5	0.5	0	1
Comparison	0.5	0.5	0	1
Classification	0.5	0.5	0	1
Organization	0.5	0.5	0	1
Planning	0.5	0.5	0	1
Problem solving	0.5	0.5	0	1
Decision making	0.5	0.5	0	1
Communication	0.5	0.5	0	1
Interpersonal skills	0.5	0.5	0	1
Teamwork	0.5	0.5	0	1
Leadership	0.5	0.5	0	1
Management	0.5	0.5	0	1
Organization	0.5	0.5	0	1
Administration	0.5	0.5	0	1
Coordination	0.5	0.5	0	1
Supervision	0.5	0.5	0	1
Control	0.5	0.5	0	1
Monitoring	0.5	0.5	0	1
Evaluation	0.5	0.5	0	1
Feedback	0.5	0.5	0	1
Improvement	0.5	0.5	0	1
Innovation	0.5	0.5	0	1
Creativity	0.5	0.5	0	1
Originality	0.5	0.5	0	1
Uniqueness	0.5	0.5	0	1
Novelty	0.5	0.5	0	1
Ingenuity	0.5	0.5	0	1
Resourcefulness	0.5	0.5	0	1
Adaptability	0.5	0.5	0	1
Flexibility	0.5	0.5	0	1
Openness	0.5	0.5	0	1
Curiosity	0.5	0.5	0	1
Enthusiasm	0.5	0.5	0	1
Optimism	0.5	0.5	0	1
Positivity	0.5	0.5	0	1
Confidence	0.5	0.5	0	1
Self-esteem	0.5	0.5	0	1
Resilience	0.5	0.5	0	1
Stress management	0.5	0.5	0	1
Emotional stability	0.5	0.5	0	1
Psychological well-being	0.5	0.5	0	1
Life satisfaction	0.5	0.5	0	1
Quality of life	0.5	0.5	0	1
Health-related quality of life	0.5	0.5	0	1
Functional status	0.5	0.5	0	1
Physical functioning	0.5	0.5	0	1
Role limitation due to physical problems	0.5	0.5	0	1
Bodily pain	0.5	0.5	0	1
General health	0.5	0.5	0	1
Energy/fatigue	0.5	0.5	0	1
Emotional well-being	0.5	0.5	0	1
Social functioning	0.5	0.5	0	1
Relationships	0.5	0.5	0	1
Family	0.5	0.5	0	1
Friends	0.5	0.5	0	1
Community	0.5	0.5	0	1
Society	0.5	0.5	0	1
World	0.5	0.5	0	1

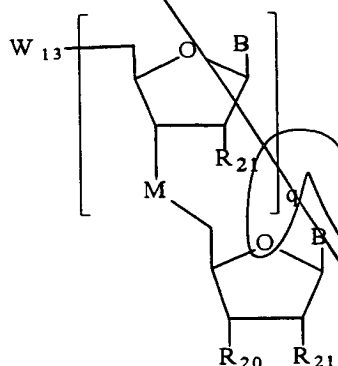
45. A compound having the formula XIII A, XIIB, XIIIC or XIIID:



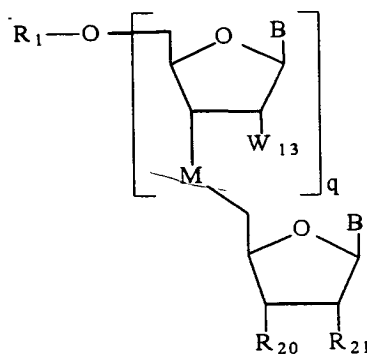
XIII A



XIIB



XIIIC

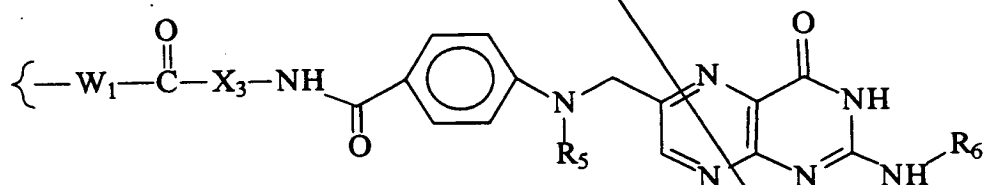


XIIID

wherein:

5

$W_{13}$  has the formula:



$R_1$  is H or a hydroxyl protecting group;

B is a nucleobase;

each  $R_{21}$  is H, OH, F, or a group of formula  $Z-R_{22}-(R_{23})_v$ ;

Z is O, S, NH or  $N-R_{22}-(R_{23})_v$ ;

$R_{22}$  is  $C_1-C_{20}$  alkyl,  $C_2-C_{20}$  alkenyl, or  $C_2-C_{20}$  alkynyl;

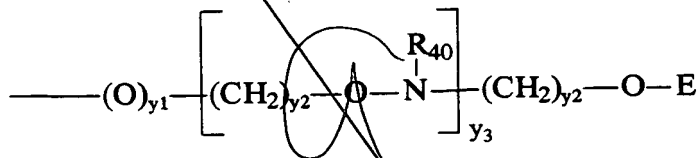
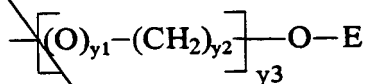
$R_{23}$  is hydrogen, amino, halogen, hydroxyl, thiol,

10



keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

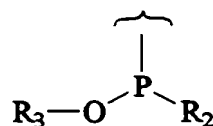
or  $R_{21}$  has one of the formulas:



wherein:

- 15             $y_1$  is 0 or 1;  
                $y_2$  is 0 to 10;  
                $y_3$  is 1 to 10;  
               E is  $N(R_{41})(R_{42})$  or  $N=C(R_{41})(R_{42})$ ;  
               each  $R_{41}$  and each  $R_{42}$  is independently H,  $C_1$ - $C_{10}$   
 20 alkyl, a nitrogen protecting group, or  $R_{41}$  and  $R_{42}$  taken together form a nitrogen protecting group; or  $R_{41}$  and  $R_{42}$  taken together with the N or C atom to which they are attached form a ring structure that can include at least one heterotom selected from N and O;  
 25            v is from 0 to about 10;  
               q is from 0 to about 50;  
               M is an optionally protected internucleoside linkage;  
                $W_1$  is a linking group, O, NH or S;

R<sub>20</sub> is H or a group of Formula:



R<sub>2</sub> is -N(R<sub>7</sub>)<sub>2</sub>, or a heterocycloalkyl or heterocycloalkenyl ring containing from 4 to 7 atoms, and 5 having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;

R<sub>7</sub> is straight or branched chain alkyl having from 1 to 10 carbons;

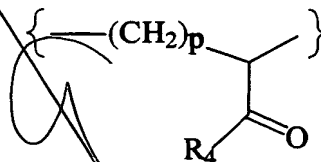
R<sub>3</sub> is a phosphorus protecting group;

10 n is from 1 to about 10;

R<sub>5</sub> is H or an amino protecting group;

R<sub>6</sub> is H or an amino protecting group;

X<sub>3</sub> is -CH(Z<sub>1</sub>)- or a group of Formula XI:



XI

Z<sub>1</sub> is the sidechain of a naturally occurring amino acid, or a protected sidechain of a naturally occurring amino acid;

p is 1 or 2; and

20 R<sub>4</sub> is a hydroxyl group, or a protected hydroxy group.

46. The compound of claim 45 wherein W<sub>1</sub> is -O-(CH<sub>2</sub>)<sub>n</sub>-NH- where n is from 1 to about 10.

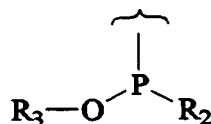
47. The compound of claim 45 wherein n is 6.

48. The compound of claim 45 wherein R<sub>1</sub> is

dimethoxytrityl,  $R_5$  is trifluoroacetyl, and  $R_6$  is  $-C(=O)-CH(CH_3)_2$ , and  $R_4$  is t-butoxy.

49. The compound of claim 45 wherein  $q$  is 0.

50. The compound of claim 45 wherein  $R_{20}$  is a group of 5 formula:



wherein  $R_3$  is  $\beta$ -cyanoethyl, and  $R_2$  is diisopropylamino.

51. The compound of claim 50 wherein  $W_1$  is  $-O-(CH_2)_6-NH-$ ,  $R_1$  is dimethoxytrityl,  $R_5$  is trifluoroacetyl,  $R_6$  is  $-C(=O)-CH(CH_3)_2$ , and  $R_4$  is t-butoxy.

52. The compound of claim 50 wherein  $q$  is 0.

53. The compound of claim 45 wherein  $X_3$  has the formula XI.

54. The compound of claim 53 wherein  $p$  is 2.

55. The compound of claim 54 wherein  $W_1$  is  $-O-(CH_2)_6-NH-$ .

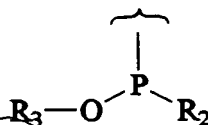
56. The compound of claim 55 wherein  $R_4$  is t-butoxy.

57. The compound of claim 56 wherein  $R_1$  is dimethoxytrityl,  $R_5$  is trifluoroacetyl, and  $R_6$  is  $-C(=O)-CH(CH_3)_2$ .

58. The compound of claim 57 wherein  $q$  is 0.

T00007 T00007 T00007

59. The compound of claim 58 wherein  $R_{20}$  is a group of formula:

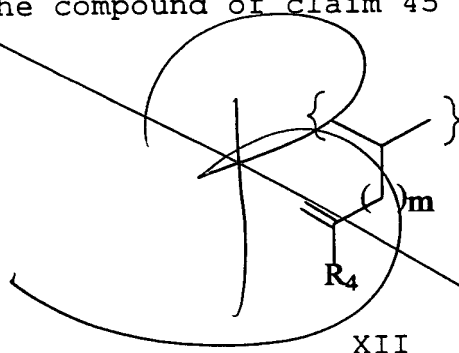


wherein  $R_3$  is  $\beta$ -cyanoethyl, and  $R_2$  is diisopropylamino.

60. The compound of claim 57 wherein  $R_{20}$  is H.

61. The compound of claim 60 wherein  $q$  is 0.

62. The compound of claim 45 wherein  $X_3$  has the formula  
XII:



wherein  $m$  is 1 or 2.

63. The compound of claim <sup>107</sup>~~62~~ wherein  $m$  is 2.

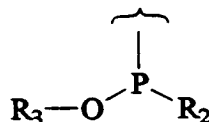
64. The compound of claim 63 wherein  $W_1$  is  
 $-\text{O}-(\text{CH}_2)_6-\text{NH}-$ .

15 <sup>Sub B6</sup> 65. The compound of claim ~~54~~ wherein  $R_4$  is t-butoxy.

66. The compound of claim 65 wherein  $R_1$  is dimethoxytrityl,  $R_5$  is trifluoroacetyl, and  $R_6$  is  
 $-\text{C}(=\text{O})-\text{CH}(\text{CH}_3)_2$ .

67. The compound of claim 66 wherein  $q$  is 0.

68. The compound of claim 67 wherein  $R_{20}$  is a group of formula:

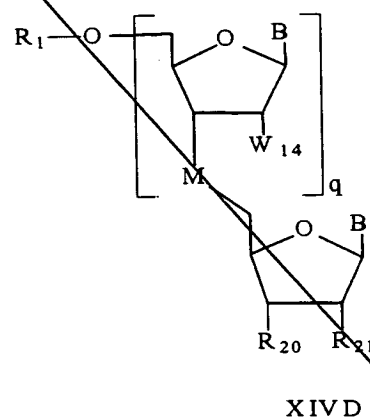
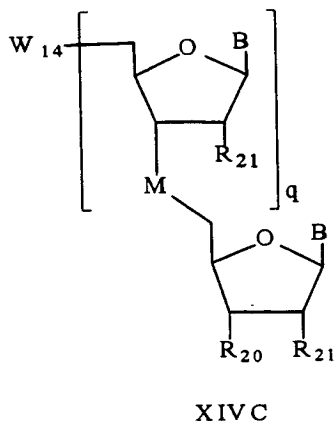
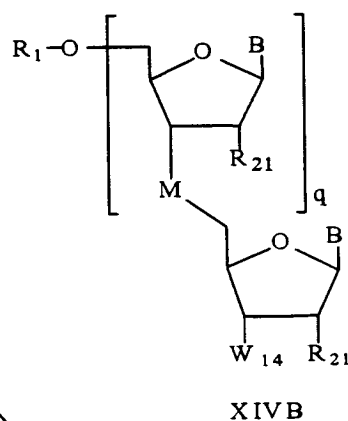
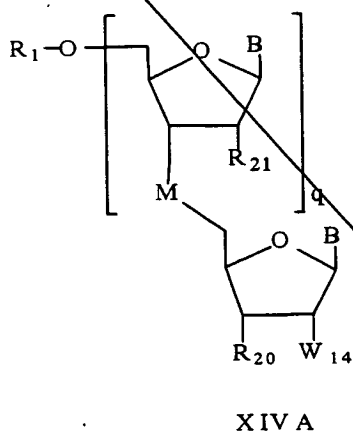


where R<sub>3</sub> is β-cyanoethyl, and R<sub>2</sub> is diisopropylamino.

5 69. The compound of claim 45 wherein R<sub>20</sub> is H.

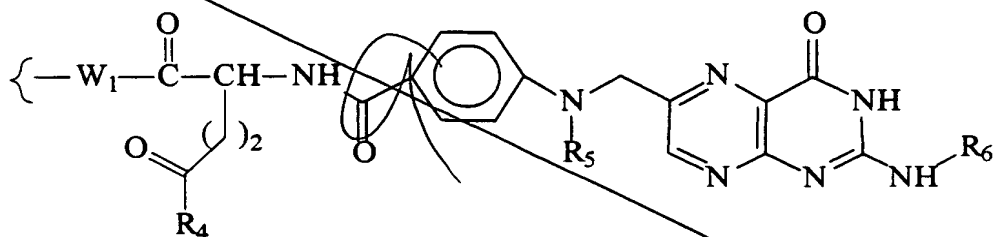
70. The compound of claim 69 wherein q is 0.

~~71. A composition comprising a compound of claim 54, said composition being substantially free of a compound of formula XIVA, XIVB, XIVC, or XIVD:~~

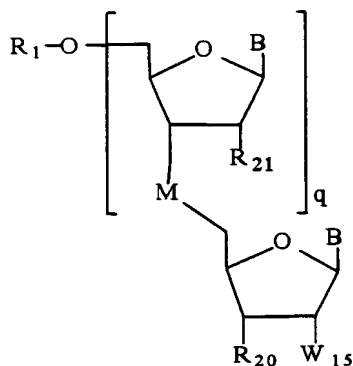


wherein:

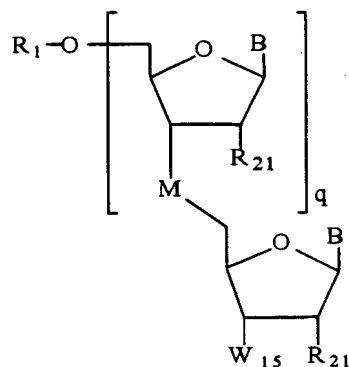
$W_{14}$  has the formula:



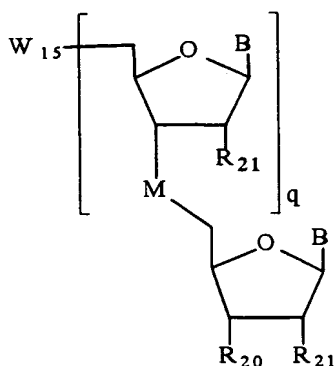
72. A composition comprising a compound of claim 63, 5 said composition being substantially free of a compound of formula XVA, XVB, XVC or XVD:



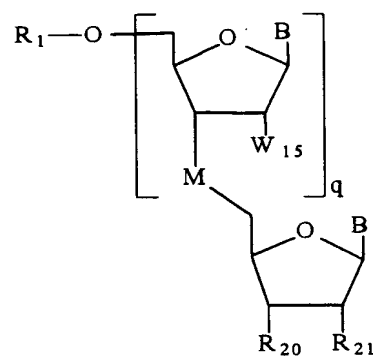
XVA



XVB

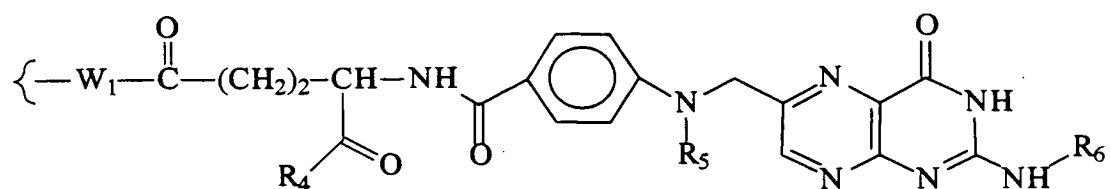


XVC

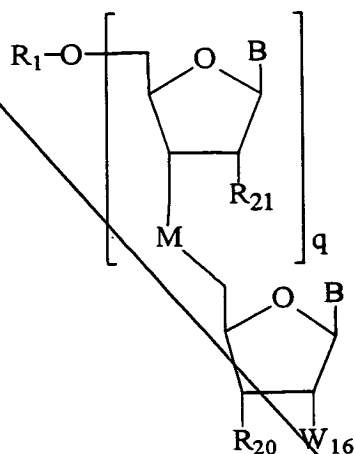


XVD

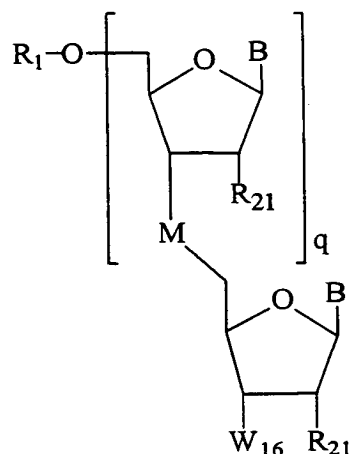
wherein  $W_{15}$  has the formula:



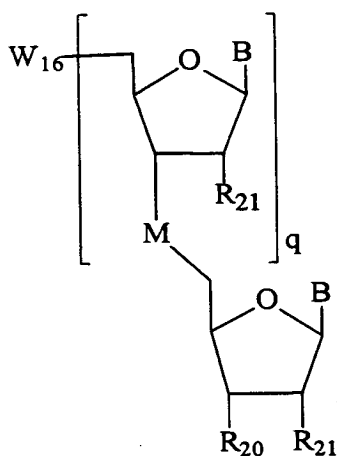
73. A compound having the formula XVIA, XVIB, XVIC or XVID:



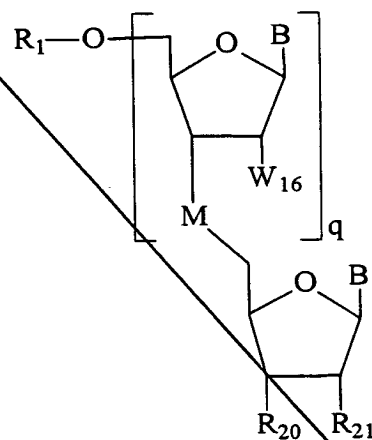
XVIA



XVIB



XVIC

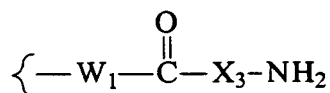


XVID

5

wherein:

$W_{16}$  has the formula:



$R_1$  is H or a hydroxyl protecting group;

B is a nucleobase;

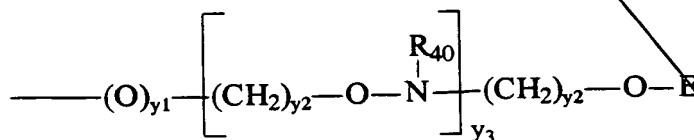
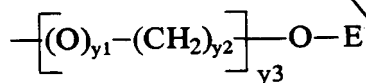
each  $R_{21}$  is H, OH, F, or a group of formula  $Z-R_{22}-(R_{23})_v$ ;

5  $Z$  is O, S, NH or  $N-R_{22}-(R_{23})_v$ ;

$R_{22}$  is  $C_1-C_{20}$  alkyl,  $C_2-C_{20}$  alkenyl,  $C_2-C_{20}$  alkynyl,  $C_1-C_{20}$  akoxyl,  $C_2-C_{20}$  alkenyloxy, or  $C_2-C_{20}$  alkynyloxy;

$R_{23}$  is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, inter-  
15 calator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleo-  
tides;

20 or  $R_{21}$  has one of the formulas:



wherein:

$y_1$  is 0 or 1;

$y_2$  is 0 to 10;

25  $y_3$  is 1 to 10;



E is  $N(R_{41})(R_{42})$  or  $N=C(R_{41})(R_{42})$ ;

each  $R_{41}$  and each  $R_{42}$  is independently H,  $C_1-C_{10}$  alkyl, a nitrogen protecting group, or  $R_{41}$  and  $R_{42}$  taken together form a nitrogen protecting group; or  $R_{41}$  and  $R_{42}$  taken together with the N or C atom to which they are attached form a ring structure that can include at least one heterotom selected from N and O;

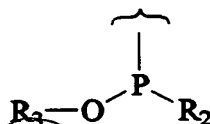
v is from 0 to about 10;

q is from 0 to about 50;

10 M is an optionally protected internucleoside linkage;

$W_1$  is a linking group;

$R_{20}$  is H or a group of Formula:



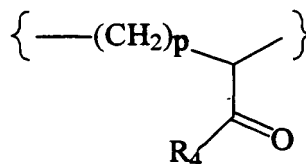
15  $R_2$  is  $-N(R_7)_2$ , or a heterocycloalkyl or heterocycloalkenyl ring containing from 4 to 7 atoms, and having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;

$R_7$  is straight or branched chain alkyl having from 1 to 10 carbons;

20  $R_3$  is a phosphorus protecting group;

n is from 1 to about 10;

$X_3$  is  $-\text{CH}(Z_1)-$  or a group of Formula XI:



XI

25  $Z_1$  is the sidechain of a naturally occurring amino acid, or a protected sidechain of a naturally occurring amino acid; and

p is 1 or 2.

74. The compound of claim 73 wherein  $X_3$  has the formula XI.

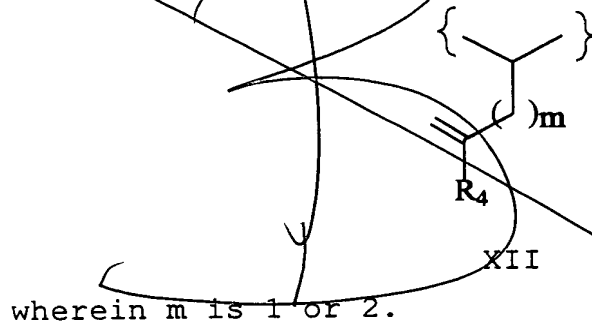
75. The compound of claim 74 wherein p is 2.

5 76. The compound of claim 75 wherein  $W_1$  is  $-O-(CH_2)_n-NH-$  wherein n is from 1 to about 10.

77. The compound of claim 76 wherein n is 6.

78. The compound of claim 73 wherein  $X_3$  has the formula XII:

10



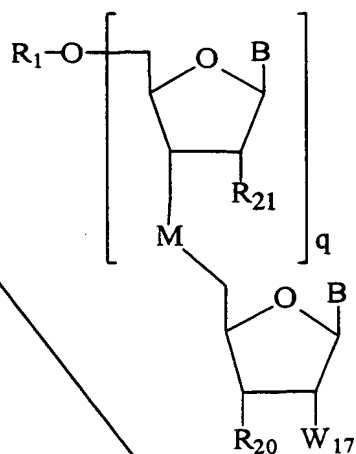
wherein m is 1 or 2.

79. The compound of claim <sup>108</sup>78 wherein m is 2.

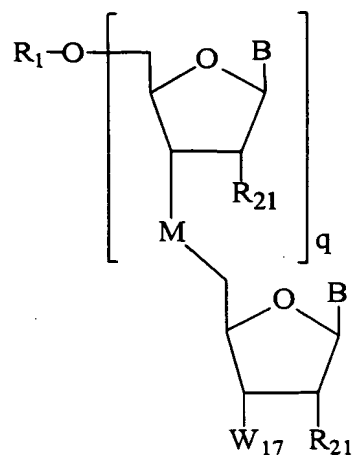
80. The compound of claim 79 wherein  $W_1$  is  $-O-(CH_2)_n-NH-$  15 wherein n is from 1 to about 10.

81. The compound of claim 80 wherein n is 6.

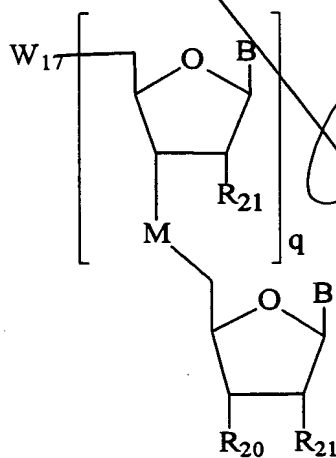
82. A compound having the formula XVIIA, XVIIIB, XVIIIC or XVIID:



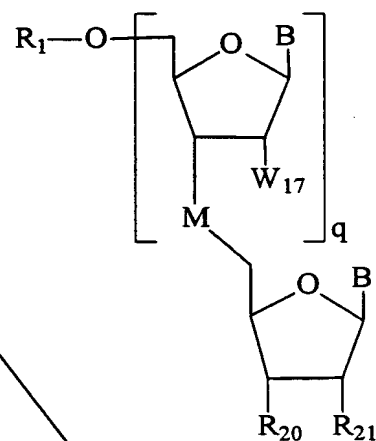
XVIIA



XVIIB



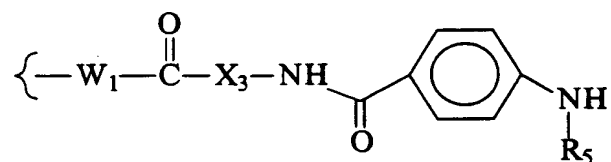
XVIIC



XVIID

wherein:

$W_{17}$  has the formula:



5

$R_1$  is H or a hydroxyl protecting group;

B is a nucleobase;

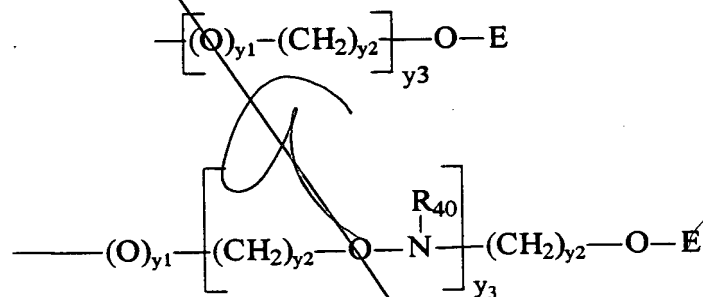
each  $R_{21}$  is H, OH, F, or a group of formula  $Z-R_{22}-(R_{23})_v$ ;

Z is O, S, NH or N-R<sub>22</sub>-(R<sub>23</sub>)<sub>v</sub>;

R<sub>22</sub> is C<sub>1</sub>-C<sub>20</sub> alkyl, C<sub>2</sub>-C<sub>20</sub> alkenyl, or C<sub>2</sub>-C<sub>20</sub> alkynyl;

R<sub>23</sub> is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

or R<sub>21</sub> has one of the formulas:



wherein:

y<sub>1</sub> is 0 or 1;

y<sub>2</sub> is 0 to 10;

y<sub>3</sub> is 1 to 10;

E is N(R<sub>41</sub>)(R<sub>42</sub>) or N=C(R<sub>41</sub>)(R<sub>42</sub>);

each R<sub>41</sub> and each R<sub>42</sub> is independently H, C<sub>1</sub>-C<sub>10</sub> alkyl, a nitrogen protecting group, or R<sub>41</sub> and R<sub>42</sub> taken together form a nitrogen protecting group; or R<sub>41</sub> and R<sub>42</sub> taken together with the N or C atom to which they are attached form a ring structure that can include at least one heterotom selected from N and O;

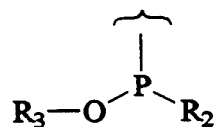
v is from 0 to about 10;

q is from 0 to about 50;

M is an optionally protected internucleoside linkage;

$W_1$  is a linking group, O, NH or S;

$R_{20}$  is H or a group of formula:



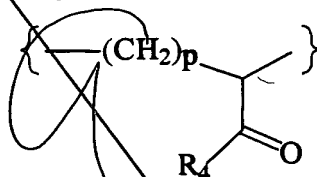
5  $R_2$  is  $-N(R_7)_2$ , or a heterocycloalkyl or heterocycloalkenyl ring containing from 4 to 7 atoms, and having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;

$R_7$  is straight or branched chain alkyl having from 1 to 10 10 carbons;

$R_3$  is a phosphorus protecting group;

n is from 1 to about 10;

$X_3$  is  $-CH(Z_1)-$  or a group of formula XI:



XI

15  $Z_1$  is the sidechain of a naturally occurring amino acid, or a protected sidechain of a naturally occurring amino acid;

p is 1 or 2; and

$R_5$  is H or an amino protecting group.

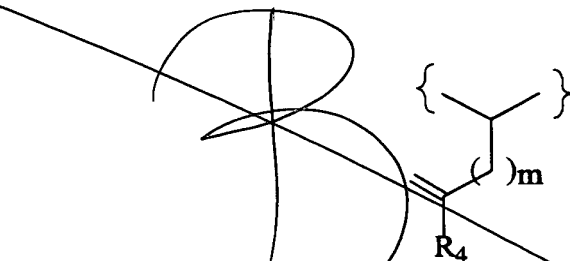
20 83. The compound of claim 82 wherein  $X_3$  has the formula XI.

84. The compound of claim 83 wherein p is 2.

85. The compound of claim 84 wherein  $W_1$  is  $-O-(CH_2)_n-NH-$  wherein n is from 1 to about 10.

86. The compound of claim 85 wherein n is 6.

87. The compound of claim 82 wherein X<sub>3</sub> has the formula XII:



XII

wherein m is 1 or 2.

88. The compound of claim <sup>109</sup>~~87~~ wherein m is 2.

89. The compound of claim 88 wherein W<sub>1</sub> is -O-(CH<sub>2</sub>)<sub>n</sub>-NH- wherein n is from 1 to about 10.

90. The compound of claim 89 wherein n is 6.

91. A folate conjugate comprising a folate moiety covalently linked to an amino acid, said amino acid further connected to a hydrocarbyl group, said hydrocarbyl group bearing at least two hydroxyl groups.

92. An oligonucleotide-folate conjugate comprising a folate moiety covalently linked to an amino acid, said amino acid being connected to a hydrocarbyl group, said hydrocarbyl group further connected to an oligonucleotide, said hydrocarbyl group bearing at least two hydroxyl groups.

93. The compound of claim <sup>101</sup>~~92~~ wherein said R<sub>4</sub> is a hydroxyl group protected with C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl or C<sub>2</sub>-C<sub>20</sub> alkynyl.

94. The compound of claim 13 wherein said R<sub>4</sub> is a

T 366 600

B

hydroxyl group protected with C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl or C<sub>2</sub>-C<sub>20</sub> alkynyl.

95. The compound of claim 16 wherein said R<sub>4</sub> is a hydroxyl group protected with C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl or C<sub>2</sub>-C<sub>20</sub> alkynyl.

96. The method of claim 19 wherein said R<sub>4</sub> is a hydroxyl group protected with C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl or C<sub>2</sub>-C<sub>20</sub> alkynyl;  
further comprising the step of deprotecting said R<sub>4</sub> with a  
10 deprotecting reagent.

97. The method of claim 96 wherein said deprotecting reagent is an aqueous amine.

98. The method of claim 97 wherein said amine is piperidine, pyrrolidine, piperazine or morpholine.

15        99.     The method of claim 96 wherein said deprotecting  
         reagent comprises an aqueous amine and a mercapto compound.

100. The method of claim 99 wherein the concentration of said mercapto compound is 2-10%.

add  
B7